REMARKS

Applicant requests reconsideration of their application in view of the foregoing amendments and the discussion that follows. The status of the claims is as follows. Claims 41-97 were previously canceled without prejudice to Applicant's filing of divisional applications to the separately patentable subject matter thereof. Claims 1-40 and 98-101 stand rejected.

Obviousness-type Double Patenting

The Examiner provisionally rejected Claims 1-40, 98-101 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-40, 97 and 98 of U.S. Patent No. 6,251,588. Applicant submits herewith an appropriate terminal disclaimer.

Rejection under 35 U.S.C. §102

Claims 1-3, 5-10, 15, 17-22, 98 and 100 were rejected under paragraph (b) of the above code section as being anticipated by Hyndman, *et al.* (Hyndman). Hyndman discloses software to determine optimal oligonucleotide sequences based on hybridization simulation data. The authors indicate that their new computer program, HYBsimulator™ (formerly OligoProbe DesignStation) creates a set of candidate oligonucleotides from a target gene. For each of the candidate oligonucleotides, a large sequence database is searched for sequences that will hybridize to the oligonucleotide. The authors refer to this as computer hybridization simulation (CHS). Using the nearest-neighbor model, the HYBsimulator takes into account mismatches in hybridization and calculates the melting temperature or free energy for hybridization to all sequences in a database. The specificity of each oligonucleotide is then quantified by the number of genes that may hybridize and the predicted melting temperatures or free energies of hybridization to those genes. The CHS data are used to select oligonucleotides based on their specificity with respect to a database.

In order to maintain a rejection under 35 U.S.C. §102(b), the Examiner must first establish a *prima facie* case of anticipation. An invention is anticipated if each and every limitation of the claimed invention is disclosed in a single prior art reference. *In re Paulsen*, 30 F.3d 1475, 1478, 31 U.S.P.Q.2d 1671, 1673 (Fed. Cir.

1994). In the present situation Freeman does not disclose each and every element of the claimed invention.

Hyndman does not anticipate the methods of Claims 1-3, 5-10, 15, 17-22, 98 and 100. There are at least the following differences between the teaching of the reference and elements of Claim 1. Hyndman does not disclose the step of identifying oligonucleotides in a subset of oligonucleotides that are clustered along a region of the nucleotide sequence that is hybridizable to the target nucleotide sequence. The present methods are based on Applicant's discovery that oligonucleotides showing high hybridization efficiencies tend to form clusters. Applicant's claimed methods reflect this discovery in that the claims recite the step of identifying oligonucleotides in the subset that are in clusters along a region of the nucleotide sequence that is hybridizable to the target nucleotide sequence. The Hyndman reference is completely devoid of any teaching in this regard.

As Hyndman explains, HYBsimulator creates a ProbeSet where the set contains all possible oligonucleotides derived for the target sequence that fit a chosen specification (page 1091, column 2, lines 14-17). Designated oligonucleotides are selected from the ProbeSet for a particular application. The specificity of probes in the ProbeSet is determined based on CHS data. CHS simulates hybridization of each probe in the ProbeSet with every sequence in a specified GenBank database. HYBsimulator performs multiple calculations for the possible sub-sequences and then selects the most favorable value (paragraph bridging pages 1091 and 1092.

Referring, for example, to Claim 1 as a typical claim, Claim 1 recites that a predetermined number of non-identical oligonucleotides within a nucleotide sequence that is hybridizable with the target nucleotide sequence is identified. The oligonucleotides are chosen to sample a length of the nucleotide sequence. For each of the oligonucleotides at least one parameter that is predictive of the ability of each of the oligonucleotides to hybridize to the target nucleotide sequence is determined and evaluated. A subset of oligonucleotides within the predetermined number of non-identical oligonucleotides is selected based on an examination of the parameter. Then, oligonucleotides in the subset are identified that are in clusters along a region of the nucleotide sequence that is hybridizable to the target nucleotide sequence. A hybridization oligonucleotide is selected for each cluster.

The Examiner argues that Hyndman describes the application of the HYBsimulator™ to identify common/census probes and equates this description to the language of Claim 1, namely, "clustered along a region"). The Examiner argues that the common/census probes are identified to all the targets of interest, i.e., same gene in related organism or related genes in the same organism or unknown varieties of a gene family. (citing the paragraph entitled "Common or Census Probes").

In the section referred to by the Examiner, Hyndman is concerned with detecting the same gene in related organisms or related genes in the same organism or to detect unknown varieties of a gene family by using a probe that identifies all know types of a particular gene family. To this end Hyndman's goal is to design a probe that detects a maximum number of the aforementioned genes. The probe must be effective under a multitude of circumstances. As Hyndman explains, in addition to his basic design (discussed above as to its lack of relevance to the present invention), users perform an additional CHS against a small database comprised of all the target genes. In a sense, Hyndman might be viewed as looking at the clustering of a number of genes with regard to one probe.

On the other hand, again referring to Claim 1, oligonucleotides in a subset are identified that are in clusters along a region of a nucleotide sequence that is hybridizable to the target nucleotide sequence, for example, a gene. This approach is the opposite of what Hyndman might be argued to teach. Hyndman's approach is in line with his stated goal of finding a single probe that is effective against a large number of genes from a number of sources. Even in this aspect of Hyndman's teaching, CHS is employed and, as explained above, CHS is a method that simulates hybridization of each molecule of interest, in this case one probe against as many of a multitude of genes as possible. The present invention, on the other hand, seeks to select good probes without performing full thermodynamic and other studies. Applicant has found that good probes can be obtained by viewing clustering of a multitude of probes along a region of a nucleotide sequence that is hybridizable to the target nucleotide sequence.

Rejection under 35 U.S.C. §103

Claims 1-3, 5-10, 15, 17-22, 98-101 were rejected under paragraph (a) of the

above code section as being unpatentable over Hyndman taken in view of Southern (U.S. Patent No. 5,700,637). The Examiner argues that it would have been obvious to someone of ordinary skill in the art at the time of the invention to practice Hyndman with Southern electronically transfer identified sequences (i.e., data) to an oligonucleotide array manufacturing system (i.e., computer) since Hyndman indicates the application of HYBsimulator to "design optimally specific DNA probes for dot blots, Southern blots, Northern blots, etc. "(i.e., oligonucleotide arrays).

Hyndman is deficient as discussed above and Southern does not cure these deficiencies. Accordingly, the presently claimed invention would not have been obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Claims 1-40 and 98-101 satisfy the requirements of 35 U.S.C. §§102 and 103. A Terminal Disclaimer is included with this submission. Allowance of the above-identified patent application, it is respectfully submitted, is in order.

Respectfully submitted,

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